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Secondary prevention and management of dyslipidaemia in patients with coronary artery disease on statin therapy in a tertiary academic centre in Johannesburg

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SECONDARY PREVENTION AND MANAGEMENT OF DYSLIPIDAEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE ON STATIN THERAPY IN A TERTIARY ACADEMIC CENTRE IN JOHANNESBURG



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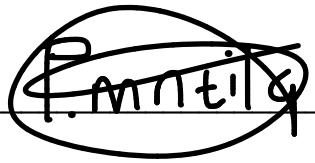
A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine.

Johannesburg, October 2023

DECLARATION

I, Dr. Patience Mtwakazi Ntila, declare that this research report (submissible article and protocol with comprehensive literature review) is my unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand. It has not been previously submitted for any other degree or examination at this or any other University.

Signature of the student



_____Date 05.10.2023_____

Name of first supervisor____Professor Nqoba Tsabedze_____



Signature _____Date_____05/10/2023_____

Name of Second supervisor_____Dr Dineo Mpanya__Date___05/10/2023__



Signature _____

DEDICATION

To God and family

And In memory of my late beloved father

Mr BV Ntila

1952 – 2017

ACKNOWLEDGEMENTS

The utmost gratitude to my supervisors for their patience and unwavering support by availing of their time and sharing their knowledge and skills. To the University of the Witwatersrand postgraduate research support faculty, for statistical guidance and the cardiology clerks, for assisting with obtaining health records. Friends and colleagues for academic and emotional support.

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RESEARCH REPORT

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Abstract

Background and aims: Low-density lipoprotein-cholesterol (LDL-C) is essential in initiating atherosclerosis, and its control is paramount in reducing future major adverse cardiovascular events. New guidelines recommend an LDL-C target of <1.4 mmol in patients with atherosclerotic cardiovascular disease. However, whether patients on statin therapy achieve these LDL-C targets in South African public hospitals is unknown. Therefore, this study aimed to determine the achievement of LDL-C targets in patients with coronary artery disease (CAD) on statin treatment at a public tertiary academic hospital.

Methods: We analysed data from 458 patients with angiographically confirmed CAD on statin therapy, comparing index admission to the most recent follow-up LDL-C level.

Results: After a median duration of 17 months (interquartile range: 7 - 31), 93 (20.3%) patients achieved the LDL-C target. Among the 329 (71.8%) patients on a high-potency statin, 76 (23.2%) achieved the LDL-C target. On univariable logistic regression analysis, a history of previous CAD or stroke [odds ratio (OR):1.73; 95% confidence interval (CI): 1.05 - 2.85; *p* value= 0.031], presentation with non-ST-elevation myocardial infarction [OR:0.55; 95% CI: 0.34 - 0.90; *p* = 0.017] and unstable angina [OR: 2.25; 95% CI: 1.08 to 4.70; *p* = 0.030] were related with failure to attain LDL-C targets.

Conclusions: Only 20.3% of all patients with atherosclerotic CAD and 23.2% on high-intensity statins achieved the guideline-recommended LDL-C target.

Keywords: low-density lipoprotein, dyslipidaemia, statin, coronary artery disease, low-and-middle-income country

1. Introduction

Globally, elevated levels of low-density lipoprotein-cholesterol (LDL-C) are estimated to cause 86.1% of deaths and disability-adjusted life years (DALYs) due to ischemic heart disease (IHD) and 13.9% due to strokes, accounting for 4.4 million deaths annually [1]. In South Africa, dyslipidaemia is estimated to affect 67.3% of the adult population above 45 [2] and 76.7% of the population receiving care for diabetes and hypertension [3]. Furthermore, It has been attributed to 59% of the IHD and 29% of the ischemic stroke burden in the adult population [4]. Sub-Saharan African countries face a growing burden of cardiovascular diseases (CVD), with CVD prevention and treatment often overlooked. Focus has been primarily placed on reducing the burden of infectious diseases [5].

A large body of evidence confirms that a critical precursor in atherosclerosis is the accumulation of LDL particles and other cholesterol-rich apo B-lipoproteins in the media of the arterial walls following previous vascular endothelial injury [6]. For every 1.0 mmol decrease in LDL-C, the incidence of major coronary events, coronary revascularisation and ischemic strokes is reduced by approximately 22% (95% confidence interval (CI): 19 - 24; $p<0.0001$) [7]. Outcomes from various clinical trials have shown a significant decrease in cardiovascular events proportional to the degree of LDL lowering without increment in side effects [8, 9, 10]. This data prompted the revision of LDL-C targets in 2019 to lower levels than usually recommended in the 2016 guidelines [11]. Lowering the LDL-C

target to even < 1 mmol may be contemplated for patients with atherosclerotic cardiovascular disease (ASCVD) who experience a recurrence of a vascular event within two years while on maximally tolerated statin-based therapy [11].

Numerous patients on statin monotherapy fail to achieve these LDL-C targets and remain susceptible to future cardiovascular events [12, 13]. Adding ezetimibe or proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors to high-intensity statin therapy significantly reduces LDL-C levels [14, 15]. Contemporary studies [16] and the 2019 European Society of Cardiology/ European Atherosclerosis (ASC/EAS) dyslipidaemia guidelines support the early use of combination therapy [11].

The ESC/EAS and AHA/ACC guidelines recommend a stepwise approach in LDL-C treatment intensification, with statins as the first line lipid lowering therapy (LLT) and Ezetimibe as the second line for patients who are either intolerant to statins or unable to attain recommended LDL-C targets on maximally tolerated doses. Adding PCSK9 inhibitors as a third-line agent is recommended in patients not attaining their LDL-C goals on second-line treatment or where any second-line treatments are contraindicated [11, 17]. High-intensity statins provide at least a 50% decrease in baseline LDL-C levels [18], ezetimibe 20 - 27% [19], while PCSK 9 inhibitors provide at least 60% reduction either as monotherapy [8, 20], or a further 46- 73% reduction in combination to a maximally tolerated statin or other LLT such as Ezetimibe [15, 21]. Combining statins with ezetimibe further reduces LDL-C by 24% [22].

Data from other low- and middle-income countries (LMIC) indicates suboptimal treatment of dyslipidaemia in patients with coronary artery disease (CAD) [23]. Several observational studies in South Africa have examined dyslipidaemia treatment across public and private healthcare patients with differing cardiovascular risk levels. However, none specifically examined LDL-C targets in the very-high cardiovascular-risk population in a tertiary public sector hospital [24, 25, 26, 27, 28]. Therefore, this study aimed to ascertain the achievement of LDL-C targets in patients with atherosclerotic CAD on statins treated in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

2. Materials and methods

2.1 Study design and sampling

The study retrospectively analysed in and outpatient medical records for 1000 consecutive patients treated at the CMJAH with angiographically proven CAD from 3 April 2017 to 31 December 2019. The availability of an angiogram report confirming atherosclerotic CAD was the first entry criterion. Patients with angiographically proven CAD and on oral statin therapy for at least six weeks, with baseline and follow-up lipograms available, were enrolled in the study. Patients with neither baseline nor follow-up lipograms, unspecified acute coronary syndrome (ACS) presentation, or not on lipid-lowering therapy (LLT) were excluded from the analysis. The final study cohort comprised 458 patients (Fig.1). We compared baseline lipograms from the index admission for ACS or

chronic coronary syndromes (CCS) with the most recently tested levels on follow-up.

2.2 Data Collection

We reviewed medical records and registers from the cardiac catheterisation laboratory, including filed and electronic coronary angiogram reports. Variables such as age, gender, medical history, type of ACS on presentation, vital signs, electrocardiogram (ECG) and echocardiography findings were captured on the Research Electronic Data Capture (Redcap) database. Demographic information was verified using the hospital Medicom register system. In addition, the National Health Laboratory online blood-results portal was used to obtain records of laboratory test results, such as HIV results, renal function tests, lipogram and glycated haemoglobin A1c (HbA1C).

2.3 Outcome measures

We defined LDL-C targets per the European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) 2019 guidelines as LDL-C $\leq$ 1.4 mmol and an absolute 50% reduction from baseline for very high cardiovascular risk [11]. All the patients in this study were categorised as having very high cardiovascular risk according to the ESC/EAS 2019 guidelines as they had established ASCVD. Hypertension and diabetes were defined according to the World Health Organization as a systolic blood pressure ≥ 140mmHg or diastolic ≥ 80mmHg, known medical history of hypertension/diabetes/diabetic treatment or an HBA1c

level above 6.5%, respectively [29, 30, 31]. Dyslipidaemia was defined according to the Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMDASA), as total cholesterol of > 5.2mmol, and or HDL <1.0mmol for males, 1.2mmol for females, triglycerides > 1.8mmol and LDL-C ≥ 2.6mmol [32], or patients on lipid-lowering medication. The estimated glomerular filtration rate (eGFR) was calculated with the modification of diet in renal disease formula (MDRD). Statin potency was categorised according to the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines of 2018 into high, moderate, to low-intensity statin therapy [33]. Simvastatin 10mg was the only low-intensity statin therapy used in this cohort, and atorvastatin 10-20mg daily or simvastatin 20-40mg daily was used for moderate-intensity statin therapy. Atorvastatin 40-80mg daily was the only high-intensity statin therapy available. High-intensity statin was freely prescribed. Ezetimibe, at the time of the study, was only attainable by referral to the lipid clinic run by the endocrinology department. Patients were assessed as compliant or non-compliant if specifically documented on the notes by the treating doctor. Family history was defined as a history of ASCVD in a first-degree relative under the age of 55 if male and 65 for females [34] and assessed as present if marked yes on the admission data.

2.4 Data Analysis

All statistical analyses were conducted on Stata statistical software version 17 (College Station, Texas: StataCorp LLC). Categorical data were outlined as absolute numbers and percentages. The data distribution was determined using

histograms and normality tests such as the skewness and the Shapiro-Wilk tests. Normally distributed data were reported using means and standard deviation and when skewed with the median and interquartile ranges. To compare normally distributed data, parametric tests such as the paired student t-test was used for continuous data, Pearson's chi-square for categorical data and the Wilcoxon rank sum test for non-parametric continuous data. Clinical parameters between patients who achieved LDL-C targets and those who failed to were compared using the t-test. Logistic regression analysis was used to identify predictors of failure to achieve LDL-C targets. Confidence intervals were set at 95%, and a *p*-value less than 0.05 was considered a threshold for statistical significance for all statistical tests. No formal power calculation was done for sample size calculation as this is a descriptive study. The sample-sized estimation was based on the average number of annual admissions in the Cardiology Department at CMJAH for patients with suspected CAD.

2.5 Ethics consideration

Ethical clearance was approved on 30 January 2020 by the University of the Witwatersrand Human Research Ethics Committee (M191183). The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki. The institution’s departments and the Gauteng Department of Health approved the research proposal.

3. Results

3.1 Baseline demographic characteristics and comorbidities

The mean age was 60 ± 11.2 years. Males comprised 328 (71.6%) of all patients, and 199 (43.4%) were Caucasians. Hypertension was reported in 325 (70.9%) patients and dyslipidaemia in 290 (63.3%) participants. A previous history of CAD/cerebrovascular accident (CVA) was prevalent in 146 (40.2%) patients who failed to attain LDL-C targets (*p*-value=0.029). The rest of the participants' baseline characteristics are presented in Table 1.

3.2 Types of statins used compliance and achievement of LDL-C levels.

There were 329 (71.8%) patients on high-intensity statin therapy, while 132 (28.8%) were on moderate-intensity statin therapy (Fig. 2). The mean dose of simvastatin used was 37.5 ± 6.9 mg daily (daily) and 73.7 ± 15.3 mg daily for atorvastatin. One patient was on combination therapy with high-intensity statin and ezetimibe. PCSK9 inhibitors were not available during the study for our patient cohort. The number of patients achieving LDL-C goals was 93 (20.3%). Of these patients who attained LDL-C targets, 76 (16.6%) were on high-intensity statin and 17 (3.7 %) on moderate-intensity statin therapy. Patients who did not achieve follow-up LDL-C targets had either an insufficient reduction in LDL-C levels to target in 232 (63.6%) patients or no change in 12 patients (3.3%) and an increase from baseline amongst 121 (33.1%) patients. Patients attaining LDL-C targets had a higher mean diastolic blood pressure (84 ± 18.1, 95% CI: 80 – 88 mmHg) than patients without a significant reduction in LDL-C levels (79 ±

16.2, 95% CI: 77 – 81 mmHg, *p*=0.016). Among all patients included in the study, 11 (2.4%) were non-compliant on medication, while in the majority (84.6%) compliance was not assessed upon review of medical records.

3.3 Laboratory parameters

Baseline lipograms are shown in Fig. 3. There were 198 (43.2%) patients with a baseline LDL-C between 3.0 to 4.89 mmol, and the mean LDL-C in the entire cohort was 3.06 ± 1.2 mmol. Patients who attained the LDL-C target had a higher mean baseline total cholesterol (TC) of 5.6 ± 1.4 mmol than those who did not, whose baseline was 4.5 ± 1.2 mmol (*p*-value <0.001).

3.4 *Univariable and multivariable logistic regression analysis*

On univariable logistic regression analysis, a previous history of CAD/CVA (OR:1.73; 95%CI 1.05 - 2.85; *p*-value= 0.031), ACS presentation with non-ST-elevation myocardial infarction (NSTEMI) (OR:0.55; 95% CI: 0.34 - 0.90; *p*-value= 0.017), and unstable angina (UA) (OR: 2.25; 95% CI: 1.08 to 4.70; *p*-value= 0.030) were associated with failure to attain LDL-C targets. On multivariable logistic regression analysis, patients with a previous history of ASCVD independently predicted failure to achieve LDL-C targets (OR: 1.67, 95% CI: 1.00 – 2.78, p=0.048). However, these results were considered statistically insignificant since the confidence interval crosses one (Table 2).

4. Discussion

In this study, we reviewed patients' medical records with atherosclerotic CAD. The key finding was the failure to achieve LDL-C targets in 79.7 % of the study population. Furthermore, only 71.8% of patients were on a high-potency statin. On univariate logistic regression, ACS presentation with NSTEMI (OR:0.55; 95% CI: 0.34 - 0.90; *p*-value= 0.017) or UA (OR: 2.25; 95% CI: 1.08 to 4.70; *p*-value= 0.030) and a previous history of ASCVD (OR:1.73; 95%CI 1.05 - 2.85; *p*-value= 0.031) was associated with failure to attain LDL-C targets. However, on multivariable logistic regression analysis, none of the clinical parameters independently predicted failure to attain LDL-C targets.

The association between ACS presentation and failure to achieve LDL-C targets on univariate regression analysis could be explained by the reluctance of treating physicians to initiate high-potency statins in ACS presentations other than ST-elevation myocardial infarction (STEMI), however, as shown in (Table 1), patients with STEMI made the majority of those who did not attain target LDL-C levels. Current evidence-based guidelines advise initiating high-intensity statins in all patients with ACS irrespective of ACS presentation or baseline LDL-C levels, supported by evidence from studies showing benefit in early high-intensity statin prescription [35, 36, 37].

Although patients who attained LDL-C targets started with higher baseline total cholesterol levels, 81.7% were on a high-intensity statin compared to 69.3% of those who failed to attain the LDL-C goal (*p*-value 0.006). Thirty per cent (30.6%) of patients who did not attain LDL-C targets were inappropriately on moderate-

intensity statins (*p*-value 0.015). Previous history of CVA/IHD was associated with failure to achieve LDL-C targets; the hypothesis which could explain this finding could be that those patients were already on statin therapy at baseline and already had uncontrolled LDL-C levels when they presented with a second cardiovascular event; hence there was not much change in their LDL-C levels at follow up. However, due to the study's retrospective nature, we could not gather that information from the patient records. High diastolic blood pressures were associated with the ability to attain LDL-C targets; however, it could have been a chance finding or perhaps due to frequent follow-ups with regular up-titration of medications, as these patients might have been deemed very high risk by clinicians due to poor blood pressure control.

Across all racial groups, most patients failed to achieve LDL-C targets, however, with the majority being Caucasian. Whether the presence of familial hypercholesterolaemia, which is more prevalent in the Caucasian population and to a lesser extent in the Asian population, was a factor that needed to be explored. Patients with FH usually have higher baseline LDL-C and find it harder to achieve LDL-C targets on statin therapy alone.[38, 39]

Although half of the patients in the study had unknown HIV status; among the 15 that were known to be HIV positive, 12 failed to attain LDL-C targets despite the majority (n=9) having LDL-C < 2.6 mmol at baseline. Studies have shown variations in lipid profiles of HIV-infected individuals compared to those who are negative, with low HDL in the dyslipidaemia range, high triglycerides, and even high LDL cholesterol have been reported inconsistently in studies [40, 41].

Moreover, the addition of protease inhibitors causes a further increase in triglycerides and LDL-C levels [40]. Our findings were also consistent with the findings of the PACS-HIV lipids sub-study, which showed that HIV-infected patients at six months follow-up after ACS had worse lipid profiles than HIV-uninfected individuals, despite having similar baseline lipids and were likely to be prescribed less potent statins [42].

Secondary lipid control in high-risk patients remains challenging, even in high-income countries (HIC) [43]. However, it is much better than in LMIC [44]. Our study findings demonstrate suboptimal achievements of LDL-C targets in these patients. A contemporary study from Poland reported a 68.1% prescription rate of high-intensity statins, which was slightly lower than in our study. However, 2.6% of their patients were on ezetimibe, and 2.2% were on a combination of statin and ezetimibe. PCSK9 inhibitors were also not available at the time of their study. Although still suboptimal, 62.7% of their study population attained LDL-C targets which was much higher than our study. Furthermore, in their study, a higher proportion of their patients had availability of baseline and follow-up LDL-C levels at 85.3 % and 80.4%, respectively, which is much higher in comparison to our study, where only 80% of baseline and 57.1% of follow-up LDL-C levels were available for the entire study population. Employment, age, loneliness, and diabetes were positively associated with attaining LDL-C targets [45].

Incomparable middle-income countries such as Thailand, higher rates of utilisation of high-intensity statins were observed. Findings from a tertiary hospital database in Thailand reported prescription rates of high-intensity statins

in 56.3% of patients with ACS, which was still lower than recommended. Moreover, attaining LDL-C targets was also low at 43,3% on subsequent follow-up. Even though the rate of a high-intensity prescription was lower than in our patients, more of their patients attained the LDL-C targets. Multiple environmental, genetic, and behavioural factors may explain the finding. Their study's ability to achieve targets was associated with low baseline LDL-C levels and usage of high-intensity statins [46].

In South Africa, Blom DJ et al. reported target LDL-C achievement in only 41.4% of their study population, predominantly private healthcare patients, and even lower at 32.3% for patients with very high cardiovascular risk. However, they enrolled 34.1% of patients with confirmed CAD and targeted LDL-C goals of <1.8mmol / 50% absolute reduction from baseline based on the 2016 EAS/ESC guidelines in practice at the time.[28] The demographic of their study population was similar to our study in age, gender, racial groups and underlying co-morbidities. Of note, the use of combination therapy with ezetimibe was also reported to be deficient at 13.8%. Monoclonal antibodies to PCSK9 were unavailable commercially [47]. Although attaining LDL-C targets was still suboptimal, these results highlight the discrepancies between our country's private and public healthcare sectors.

The prospective epidemiological survey (PURE) findings showed higher statin prescription rates in high-income countries at 66.5 % relative to 3.3% in low-income countries. South Africa was in the upper middle-income range. Lower middle-income countries had lower statin utilisation compared to upper middle-

income countries. The low utilisation rate in Africa includes Zimbabwe. Variations were also noted between the urban and rural populations, especially in poorer countries. [44]. South Africa has the lowest rates of statin prescription and utilisation, and even those on treatment, 48% fail to reach LDL-C targets [26].

Studies from developed countries have reported a reduced likelihood of LLT prescription or attainment of LDL targets in females compared to males and in the elderly population above 75 [48, 49]. However, in this study, there were no gender differences, and the mean age of participants was younger (60 ± 11.2 years). Both genders comprised 78 to 80% of the patients who failed to attain LDL-C targets within their respective groups.

An interplay between various physicians, medication and patient-related factors could have contributed towards the failure to attain the LDL-C goal. Possible physician-related contributory factors are failure to initiate high-intensity statin on all patients irrespective of ACS presentation or baseline lipid levels, the inertia to actively titrate LLT at follow-ups, lack of knowledge of guidelines regarding LDL-C targets and CV risk estimation [50], reluctance to use and inaccessibility of non-statin combination therapies [51]. Patient and socioeconomic or drug-related factors such as non-adherence [52], statin intolerance, and economic and geographical hindrances to access health care were also possibilities [53, 54]. Moreover, variability in statin metabolism has been reported to be shared amongst the general population [55, 56].

Despite various studies showing the incremental lowering of LDL-C with combination therapy using statins and PCSK9 inhibitors or ezetimibe [8, 14, 15], access and cost remain significant limitations to their use in LMIC. Patients attending public sector facilities only have access to low and moderate-intensity statins. They would require a referral to tertiary/quaternary hospitals or specialist lipid clinics to attain high-intensity statin and ezetimibe. Ezetimibe is only accessible to patients referred to lipid clinics. With few such clinics in the country and specialists, most patients, especially in rural communities, are often disadvantaged. Furthermore, the South African 2019 National Department of Health guidelines primarily used in primary health care clinics, general practitioners' offices and secondary hospitals only recommend 10mg of atorvastatin and 40mg of simvastatin for secondary prevention of dyslipidaemia [57]. They do not promote active monitoring of LDL-C levels nor highlight the active process of dyslipidaemia management in these patients.

There is a need for easy access to additional non-statin lipid-lowering therapy, such as Ezetimibe and PCSK9 inhibitors, as many patients fail to attain treatment targets despite the high utilisation of high-intensity statins. Furthermore, patients with CAD still have a residual risk of MACE despite attaining LDL-C targets due to endothelial dysfunction caused by chronic inflammation [58]. There is promising data from new agents under review, such as colchicine.[59]

While the sample size analysed in our study was relatively small, the findings could still provide valuable insight into the level of standard practice in other South African tertiary hospitals. However, it may differ for regional and district

hospital levels of care. Therefore, multicentre large-scale quantitative research needs to be conducted to assess the adequacy of lipid management in South Africa, ascertain the possible benefits of non-statin lipid-lowering therapy, and attempt to curb the rising mortality and morbidity from cardiovascular diseases.

Although there were many missing records, such as angiogram reports, outpatient files, and admission records which led to the exclusion of a substantial number of patients, this is one of few studies from LMIC reporting attainment of LDL-C targets in very high-risk patients with ASCVD. This study happened during the transition from the 2016 to 2019 EAS/ESC guideline. Although we included patient data from 2018 and 2017, we chose the 2019 EAS/ESC LDL-C targets as various trials done before the update of the guideline showed benefits in further reductions in LDL-C targets.

We could not exclude non-compliance as a factor, as generally doctors usually document compliance status in patients with a prior history of defaulting medication. Furthermore, in patients with a prior history of atherosclerotic cardiovascular disease (cerebrovascular accident or myocardial infarction), it was not stated in their files as to whether they were already on statin therapy or not at the time of admission for an acute coronary syndrome, and due to the retrospective nature of the study we were unable to gather that information. Additionally, we did not assess for familial hypercholesterolemia as it was beyond the scope of the study (FH); achieving LDL-C targets in this population often requires a combination of LLT, which was not readily accessible in our study setting.

Conclusion

Guideline-recommended LDL-C target remains suboptimal at 20.3% in our study population, with high-intensity statins prescription in only 329 (71.8%) patients. More research is essential to ascertain the efficacy and cost-effectiveness of combination LLT in LMIC. Our recommendations strongly emphasise primary prevention and updating formularies and government guidelines. Furthermore, encouragement of healthcare personnel to follow up and manage LDL-C levels actively, nationwide availability of high potency statin therapy even at primary healthcare centres and early referral guidance to appropriate specialists for patients failing to attain LDL-C targets on appropriate statin therapy. In addition, training the healthcare personnel in primary and secondary healthcare centres is critical, as most patients eventually get discharged from cardiology care for long-term follow-ups elsewhere.

Conflict of Interest

NT is a cardiologist and has received consultation fees from Acino Health Care Group, AstraZeneca, Boston Scientific, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Sanofi, Phillips, Servier, Takeda, and Merck. He has also received educational and travel grants from Medtronic, Biotronik, Boston Scientific and Vertice Health Care Group. However, none of the other authors has any relevant financial or professional disclosures.

Author's Contributions

PN was involved in the study design, data collection, statistical table compilation, and manuscript writing. In addition, NT and DM predefined the research question and assisted in the protocol design, data analysis and revision of the manuscript.

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FIGURES AND TABLES

Fig.1. Study's flow chart. LDL-C, Low-density lipoprotein cholesterol; ACS, Acute coronary syndrome

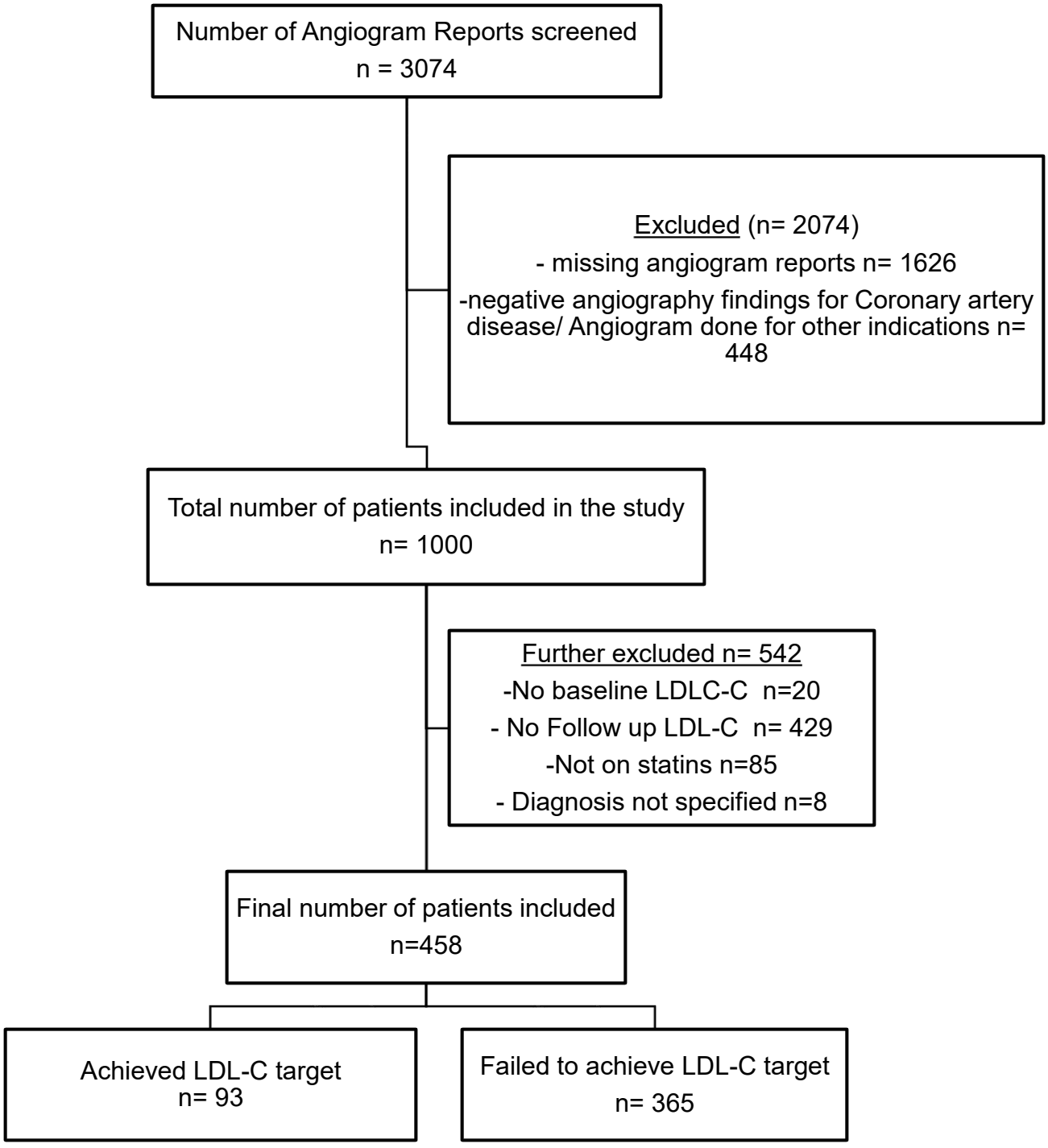


Table 1. Baseline features of the study population

Variable	Overall study participants N = 458	Target LDL-C achievement		*p-value*
		Yes N = 93 (20.3)	No N= 365 (79.7)	
(A) Demographics (%)				
Age, years (mean, SD)	60 ± 11.2	59 ± 11.0	60 ± 11.2	*0.4339*
Male (%)	328 (71.62)	65 (69.89)	263 (72.05)	*0.680*
(B) Ethnicity (%)				
Caucasian	199 (43.4)	38 (40.9)	161 (44.1)	0.*334*
Asian/Indian	128 (27.9)	32 (34.4)	96 (26.3)	
African	85 (18.6)	18 (19.3)	67 (18.4)	
Mixed Ancestry	45 (9.8)	5 (5.4)	40 (11.0)	
(C) CV risk factors (%)				
Hypertension	325 (71.0)	61 (65.6)	264 (72.3)	*0.201*
Previous CV event (stroke or CAD) (*n=456*)	172 (37.7)	26 (28.0)	146 (40.2)	*0.029*
Diabetes mellitus	172 (37.5)	34 (36.6)	138 (37.8)	*0.824*
Dyslipidaemia	290 (63.3)	62 (66.7)	228(62.5)	*0.453*
Smoker	299 (65.3)	58 (62.4)	241 (66.0)	*0.508*
PVD	16 (3.5)	4 (4.3)	12 (3.3)	*0.635*
Family history of CAD	181 (39.5)	29 (31.2)	152 (41.6)	*0.065*
CKD	66 (14.4)	8 (8.6)	58 (15.9)	*0.074*

HIV *(n=239)*	15 (3.3)	3 (3.2)	12 (3.3)	*0.976*
(D) Clinical parameters: Vital signs; median (IQR), mean				
Heart rate (b/min)	74 (IQR: 66-86)	74 (IQR: 66-90)	74 (IQR: 66-86)	0.9307
SBP (mmHg)	124(IQR: 112-141)	124 (IQR: 111-150)	124 (IQR: 112-140)	0.5086
DBP (mmHg), SD	80 ± 16.7	84 ± 18.1	79 ± 16.2	0.0106
(E) Median follow-up from baseline to follow-up lipogram				
(IQR, months)	19.9 ± 15.3	18.8 ± 14	20.2 ± 15.6	*0.6538*
(F) Baseline lipogram (mean/SD)				
Total cholesterol (mmol/L)	4.7 ± 1.3	5.6 ± 1.4	4.5 ± 1.2	*0.001*
HDL (mmol/L)	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	*0.0782*
TG (mmol/L)	1.7 ± 1.1	1.7 ± 1.5	1.7 ± 1.2	*0.9903*
LDL-C (mmol/L)	3.06 ± 1.21	3.06 ± 1.17	2.35 ± 1.10	*0.6538*
(G) Type of ACS/CAD on presentation (%)				
STEMI	186 (40.6)	39 (41.9)	147 (40.3)	*0.771*
NSTEMI	118 (25.7)	33 (35.5)	85 (23.3)	*0.016*
Unstable angina	80 (17.5)	9 (9.7)	71 (19.4)	*0.027*
Stable angina	74 (16.2)	12 (12.9)	62 (17.0)	*0.340*
(H) Chronic medication (%)				
Anti-hypertensives	438 (95.6)	91 (97.8)	347 (95.1)	*0.241*

Oral hypoglycaemic agent	143 (31.2)	27 (29.0)	116 (31.8)	*0.610*
Insulin	46 (10.0)	6 (6.4)	40 (11.0)	*0.197*
(l) lipid-lowering therapy (%)				
High-intensity statin (%)				
Atorvastatin 40-80mg	329 (71.8)	76 (81.7)	253(69.3)	*0.006*
Moderate-intensity statin (%)				
Atorvastatin 10-20mg	6 (1.3)	0 (0.0)	6 (1.6)	
Simvastatin 20-40mg	123 (26.9)	17 (18.3)	106 (29.0)	0.*015*
Compliant on treatment (*n=70*)	59 (12.9)	15 (16.1)	44 (12.0)	*0.663*

CAD; coronary artery disease, CV; cardiovascular, PVD; peripheral vascular disease, CKD; chronic kidney disease, HIV; Human immune-deficiency virus, SBP; systolic Blood Pressure, DBP; diastolic Blood Pressure, Lab; Laboratory, eGFR; estimated glomerular filtration rate, HDL; high-density lipoprotein, LDL; low-density lipoprotein, TG; triglycerides, STEMI; ST-elevation myocardial infarction, NSTEMI; non-ST elevation myocardial infarction, IQR; Inter-quartile range.

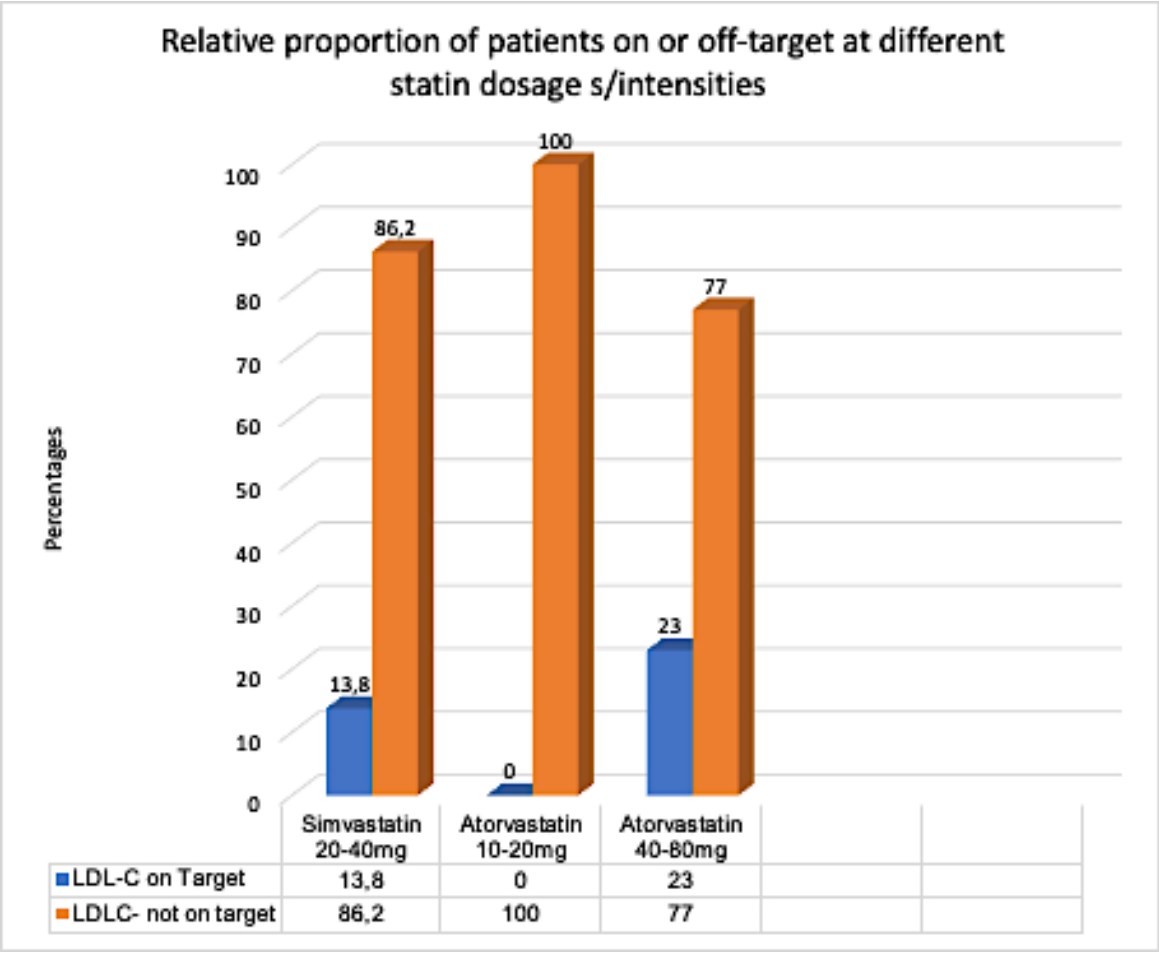


Fig 2. Distribution and potency of lipid-lowering therapy. LDL-C: low-density lipoprotein cholesterol.

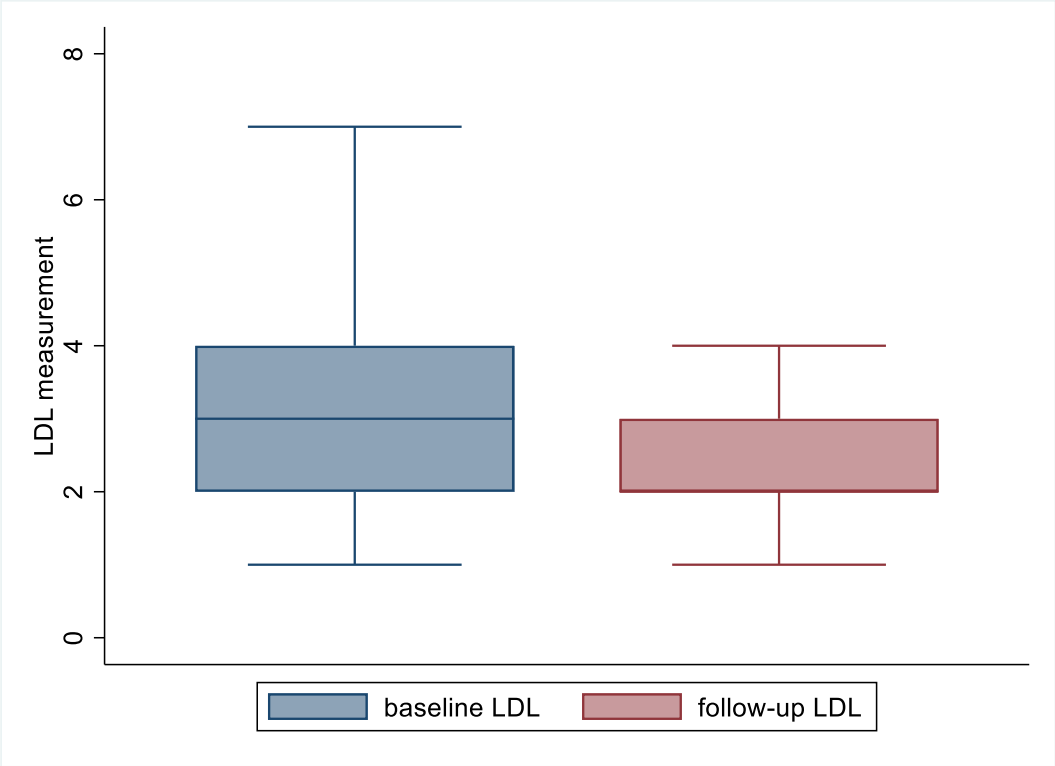


Figure. 3(a). Box-and-whiskers diagram showing pre- and post-treatment LDL-C levels after a median duration of 19.9 ± 15.3 months.

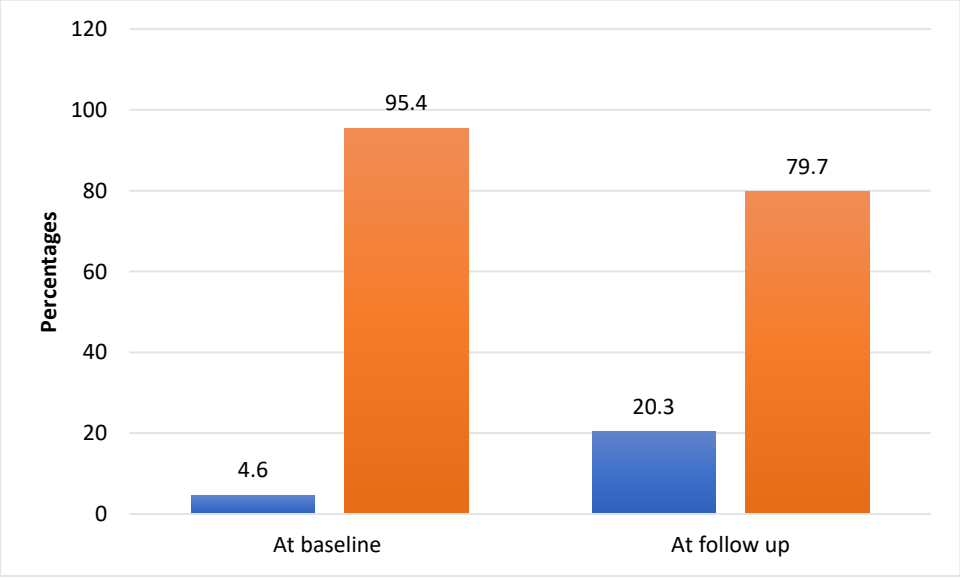


Figure.3(b). Percentage of patients with target LDL-C levels pre- and post-treatment

Table 2. Univariable and multivariable logistic regression analysis for predictors associated with failure to attain LD-C targets.

Univariable analysis			Multivariable analysis	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Family history of CAD	1.57 (0.97 – 2.56)	0.067		
History of CAD/CVA	1.73 (1.05 – 2.85)	0.031	1.67 (1.00 – 2.78)	0.048
CKD	2.00 (0.92 – 4.37)	0.079		
HDL-C	0.69 (0.40 – 1.21)	0.196		
Unstable angina	2.25 (1.08 – 4.70)	0.030	1.71 (0.79 – 3.69)	0.169
NSTEMI	0.55 (0.34 – 0.90)	0.017	0.61 (0.36 – 1.01)	0.055

OR Odds ratio, CI; confidence interval, CAD; coronary artery disease, ASCVD; atherosclerotic cardiovascular disease; CVA; cerebrovascular accident, CKD; chronic kidney disease, NSTEMI; non-ST-elevation myocardial infarction.

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Secondary prevention and management of dyslipidaemia in patients with coronary artery disease on statin therapy in a tertiary academic centre in Johannesburg

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1. LITERATURE REVIEW

In 2019, an estimated 17.9 million deaths globally (32%) resulted from cardiovascular disease (CVD) [31, 60], with 16% of the total deaths particularly due to ischemic heart disease (IHD). Of these deaths, 85% were attributed to heart attack and stroke. Most (over three-quarters) CVD deaths occur in low-middle-income countries. Of the premature deaths (i.e., death in populations under 70 years), 38% were due to CVD, and a higher proportion occurred in low-and-middle-income countries. Metabolic risk factors (such as high BMI, high blood sugar, high blood pressure, and high cholesterol) have risen by 1.5% a year since 2010 and have collectively accounted for nearly 20% of total disability-adjusted life years (DALY's) worldwide in 2019, 50% higher than in 1990 (10.4%). Furthermore, they were also responsible for a large number of deaths globally, with high blood pressure contributing to 1 in 5 deaths (almost 11 million) in 2019, high blood sugar (6.5 million deaths), high BMI (5 million), and high cholesterol (4.4 million) [61]. According to the World Health Organization's projections, NCDs will increase to 55 million by 2030 if the current conditions prevail. The greatest increase is predicted to occur in the WHO regions of Africa, South East Asia and the Eastern Mediterranean, over 20%.[62]

1.1 Burden of Disease in South Africa and Sub-Saharan Africa

South Africa is a multi-ethnic society with many cultures and lifestyles at different epidemiologic transitions, from urban westernised to remote rural regions. In all ethnicities, cardiovascular disease is a major cause of mortality and morbidity [63]. According to South African mortality statistics released in 2018, diseases of the circulatory system have increased from 17.4% in 2014 to 18.5% in 2016 and were the

top-ranking group of deaths from natural causes. Cerebrovascular accidents and Heart diseases ranked 3rd on the top leading natural causes of death behind tuberculosis and diabetes, at 5.1% [64].

In Sub-Saharan Africa, approximately 80 people die of myocardial infarction or heart failure daily [65]. In addition, more premature acute myocardial infarctions (Under age 70) occur in Sub-Saharan Africa, reflecting a lack of prevention, early detection, and effective management of cardiovascular risk factors, particularly in the black population. Furthermore, with increasing urbanisation and adopting a Westernised lifestyle, the prevalence of coronary artery disease (CAD) and the incidence of CAD-related death will likely continue to increase [66]. Therefore, a timely institution of effective management of cardiovascular risk factors is essential to curb the epidemic.

1.2 Pathology and pathophysiology of atherosclerosis

Atherosclerosis remains the major cause of mortality and premature morbidity in developed countries; however, it is projected to be the leading cause of the global disease burden globally by 2030[62]. Atherosclerosis occurs in the vasculature and can preferentially affect any region in the body, some more than others e.g., cerebrovascular accident and coronary artery disease which occur more commonly than mesenteric ischemia. Its clinical manifestations vary according to the site involved, e.g., myocardial infarction in the coronary arteries and cerebrovascular accidents in the central nervous system. Inflammation plays a big role in atherosclerosis from its inception and development to its ultimate endpoint of thrombotic complications [67]. Atherosclerosis has been extensively studied and found to be associated with chronic inflammation of the arteries, often developing over

decades in response to biological risk factors such as hypertension, smoking, obesity, insulin resistance and dyslipidaemia which lead to endothelial dysfunction. Inflammatory changes in the endothelium cause adhesion molecule VCAM-1 to be expressed, attracting monocytes. Blood-borne monocytes and cholesterol-containing LDL particles enter and migrate through the endothelial layer into the arterial intima. After undergoing further inflammatory changes, the blood-borne monocytes transform macrophages, engulf lipids, and become foam cells. This results in further inflammation and biochemical modifications, which cause endothelial and smooth muscle cell proliferation associated with the production of extracellular matrix molecules, forming a fibrous cap on the developing atheromatous plaque [68]. The plaque eventually causes a flow limiting-stenosis which may lead to angina in the coronary arteries. A complicated atheromatous plaque may then rupture thus provoking a thrombus that interrupts blood flow temporarily, leading to an acute coronary syndrome which clinically can present as either ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction or unstable angina. This is a complex process as many plaques will never obstruct the lumen but may still cause acute events either through fissuring or rupture.

A large body of data has demonstrated the role of LDL-cholesterol in atherogenesis. Most research has focused on elevated low-density lipoprotein and total cholesterol, as lifestyle changes and drug therapies can modify these. Strong, compelling evidence from multiple randomised controlled trials suggests that reducing the total cholesterol and LDL-C can prevent cardiovascular diseases [69].

1.3 Lipid metabolism

Cholesterol and triglycerides circulate in the blood in lipoprotein particles containing phospholipids and apoproteins. Apolipoproteins are genetically determined components of lipoproteins which influence conformation, receptor binding and metabolism of lipoproteins. Furthermore, they can exchange between different lipoprotein molecules. Apoproteins are classified into five categories which are A, B, C, D and E. [70]

Lipoproteins transport poorly soluble lipids (mainly triglycerides, cholesterol, and fat-soluble vitamins) from the gastrointestinal tract through various body compartments. Plasma lipoproteins are divided according to density into five groups (from least to highest density): chylomicrons, very low-density lipoproteins, intermediate-density lipoproteins, and low-density lipoproteins and high-density lipoproteins [71]. Lipoprotein metabolism can be divided into endogenous and exogenous pathways. The exogenous pathway begins with intestinal absorption of cholesterol and fatty acids by intestinal cells, in which glycerol and fatty acids are combined to form triglycerides, and the cholesterol esterified by acyl-coenzyme A. ACAT-Two Is responsible for esterification in the intestine. Triglycerides and cholesterol are assembled as chylomicrons intracellularly and transported into the circulation via the mesenteric lymphatic system into the liver. When lymph triglyceride is greater than 1.5- 3.0 mg/ml, most triglyceride is transported in larger chylomicron-sized particles, while at lower rates, smaller chylomicrons or intestinal VLDL predominate in the lymph.[72]

The endogenous pathway starts in the liver with the synthesis of VLDLs. Lipolysis happens in the capillaries with lipoprotein lipase bound to endothelial cells. During lipolysis, the lipoprotein lipase hydrolyses the VLDL particles to IDLs. In the process,

free fatty acids are released, which can be used as a source of energy, converted into triglycerides, or stored in adipose tissue. The remnant VLDL particles can either be cleared from the circulation by the LDL or remnant receptors or remodelled by hepatic lipase to form LDL-C particles. The LDL particles are then internalised by hepatic and non-hepatic tissues or converted into bile acids and secreted into the intestinal lumen. Cholesterol is secreted into bile either directly or after conversion into bile acids. Cellular requirements regulate the internalisation of LDL through a negative feedback control [71].

1.4 Role of LDL-C in Atherogenesis

The LDLR (LDL receptor) family comprises a group of endocytic receptors on the cell surface, which bind and internalise extracellular ligands, including lipoproteins, exotoxins, and lipid-carrier complexes. LDLR-mediated endocytosis is important for lipoprotein clearance, and its defect is a major cause of familial hyperlipidaemia and a fundamental risk factor for cardiovascular disease.[73] Chemically modified circulating LDL-C particles cannot be taken up by Apo B/E receptors and can thus enter macrophages and other tissues through the unregulated scavenger receptor (e.g. CD 36), resulting in excess accumulation of intracellular cholesterol and foam cell formation, contributing to the formation of an atheromatous plaque [74]. Elevated LDL can induce the development of atherosclerosis even in the absence of other risk factors. The oxidised LDL particle also acts as a chemoattractant for monocytes by increasing monocyte binding. These monocytes ultimately mature into tissue macrophages, reducing macrophage mobility and trapping the macrophages within

the vessel wall. The LDL particles also stimulate the macrophage-mediated release of cytokines and antibody formation, thus promoting inflammation [75]. Disruption of the endothelium-dependent vasodilation ensues [76].

1.5.1 Overview of acute coronary syndromes

Coronary artery disease (CAD) is defined by an obstructive atherosclerotic plaque, which causes a blood flow reduction to the myocardium. Acute coronary syndrome (ACS) is an umbrella term used to describe conditions of acute myocardial ischemia resulting from the occlusion of a coronary artery. The diagnosis of ACS is largely clinical, relying on history, electrocardiographic findings, and cardiac biomarkers of myocardial injury [77]. The fourth universal definition of myocardial injury (MI) requires evidence of a rise and fall in cardiac troponin values with at least one value above the 99th percentile upper reference limit with at least one of the following criteria [78];

- Symptoms of myocardial ischaemia.
- New ischaemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.
- Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs).

Based on the ECG, patients can be stratified into two primary groups; those with ST-segment elevation in 2 contiguous leads or new bundle branch blocks with ischemic repolarisation pattern are classified as ST-segment elevation MI (STEMI), and those

with non-ST-segment elevation (NSTEMI) ACS. Patients with STEMI generally have an occluded major coronary artery and benefit from rapid reperfusion therapy with percutaneous revascularisation or administration of intravenous fibrinolytic therapy. Patients whose initial ECG does not reveal ST-segment elevation are further subdivided into two groups based on measurement of biomarkers of ischemic myocardial injury and necrosis, into NSTEMI if positive biomarkers or unstable angina if biomarkers do not fulfil the criteria for MI. Patients ruled out for MI with normal cardiac biomarker values (≤99th percentile) may have unstable angina or an alternative diagnosis.

1.6 Role of HIV in Atherosclerosis

Beyond traditional CVD risk factors, human immunodeficiency virus (HIV) specific issues such as exposure to antiretroviral therapy, chronic inflammation, and immune activation may contribute to the increased CVD risk observed in people living with HIV [79, 80]. The Strategies for Management of Anti-Retroviral Therapy trial (SMART) compared individuals who were randomly assigned to receive continuous antiretroviral therapy with those who were randomly assigned to receive intermittent therapy based on maintaining CD4+ T-cell counts >250 cells/mm^3 [81]. Those who received continuous treatment had a lower risk of developing cardiovascular disease. Across the entire study population, elevated levels of interleukin six and D-dimers at baseline were strongly associated with an increased mortality risk. While plasma IL-6 and D-dimer levels in treated HIV-infected individuals were marginally higher than those in HIV-uninfected individuals, their impact on the subsequent risk of mortality and cardiovascular disease appeared much greater in the HIV-infected population. This observation may suggest that inflammation plays a greater role in the pathogenesis of

cardiovascular disease in the HIV-infected population than in the general population. Other observational studies in HIV-infected individuals have reported similar findings [82]. Furthermore, initiating highly active antiretroviral therapy is associated with increased total cholesterol and LDL-C levels.[83] Despite the higher prevalence of HIV in South Africa, the high incidence of ACS and stable CAD is still not observed in people living with HIV.

1.7.1 Benefits of LDL cholesterol lowering

Every 1.0mmol/l (40mg/dl) reduction in LDL-C has been associated with a corresponding 10% reduction in CVD mortality, 20% reduction in all-cause mortality, 23% reduction in major cardiac events and 17% reduction in stroke [84]. Based on this evidence, European Society of Cardiology guidelines recommend that a target LDL-C of less than 1.4 mmol and 50% absolute reduction of LDL-C from baseline confers significant risk reduction [11]. However, newer trials have shown benefits in further lowering the LDL-C below current targets, which raises the question of how low the target LDL-C should be to achieve maximum morbidity and mortality benefit.

1.8 Current therapies in secondary dyslipidaemia management

In 2018, the South African Heart Association and the Lipid and Atherosclerosis Society officially adopted the European Society of Cardiology guidelines (2016) to prevent cardiovascular disease and manage dyslipidaemia, to improve on previous guidelines, which were later updated in 2019 according to the new ESC/EAS 2019 lipid guidelines

[66]. According to the new guidelines, the treatment target for LDL-C in patients with established CVD or a very high 10-year cardiovascular risk score of more than 30% (according to the Framingham risk score) is 1.4 mmol/L and 50% absolute reduction from baseline. Current clinical management recommendations include; lifestyle modification (low-fat diet and exercise), treatment with high-intensity statins, ezetimibe (currently not easily accessible in the South African state health sector and needs specialist motivation) for an add-on to statins or in patients intolerant to statins or in whom statins are contra-indicated [85].

Results from intensive statin therapy trials have demonstrated that high-intensity statin treatment confers an additional reduction in the LDL-C compared to normal dosing (e.g., atorvastatin 40mg - 80mg instead of 20mg), thus reducing further cardiovascular events [86]. The benefits of statins in secondary prevention have been demonstrated; however, new lipid-modifying drugs have been sought due to the risk of residual cardiovascular events and side effects of high-dose statins [87]. From previous studies, approximately 10 to 20% of patients developed statin intolerance, and discontinuation of therapy is common [88]. The most common side effects previously stated were myopathy, rhabdomyolysis, transaminitis and the rarest yet controversial serious side effect the development of new-onset diabetes and haemorrhagic stroke. Although some patients with statin-associated muscle symptoms experience marked elevation in serum creatine kinase (CK) levels, most do not. Accordingly, diagnosis of this disorder remains largely subjective, based on the presence of patient-reported symptoms [89]. In the recent SAMSON study (Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment) cessation of medication for statins was as frequent for placebo, as well as symptom intensity [90]. Although hepatotoxicity has

been a previous concern when using statin therapy, data suggest that statins are safe and that levels of liver enzymes do not need to be checked routinely [91].

1.8.1 Non-statin lipid-lowering agents

Ezetimibe is a non-statin lipid-lowering agent that works by inhibiting the intestinal uptake of dietary and biliary cholesterol at the level of the brush border of the intestine via the Niemann- Pick C1 Like 1 (NPC1L1) receptor, thus reducing cholesterol delivery to the liver. The liver then reacts by upregulating the expression of LDL receptors, increasing LDL-C clearance from circulation. Clinical trials have shown a 15-22% reduction in LDL-C in patients on ezetimibe as monotherapy, with an additional 15-20% reduction with concurrent statin use [92].

1.8.2 Newer agents: PCSK/9 inhibitors

In 2003, Abifabel and colleagues discovered a gain-of-function mutation in proprotein convertase subtilisin/kexin type 9 as a novel cause of autosomal dominant hypercholesterolaemia associated with premature coronary heart disease. Soon after, mutations in PCSK9 resulting in loss of function mutations were noted to be associated with low LDL-C and protective against CAD. PCSK9 is highly expressed in the liver and binds to LDL receptors, promoting internalisation and degradation of the LDL receptor in hepatic lysosomes. LDL receptor recycling is promoted by inhibiting this process, thus increasing the functional half-life and reducing apo B-containing lipoproteins [93]. Monoclonal antibodies that inhibit PCSK9 have since emerged and effectively lower LDL-C by approximately 60%, significantly reducing cardiovascular outcomes. Preclinical and initial studies have shown that monoclonal

antibodies against PCSK9 produce rapid and sustained (over several weeks) clearance of unbound systemic PCSK/9, even after a single dose[88]. Initial studies with PCSK9 monoclonal antibodies were conducted with fully human PCSK9 monoclonal antibodies, REGN27, on healthy volunteers and shortly after with Evolocumab, then Bococizumab. Alirocumab and Evolocumab (both fully human monoclonal antibodies) have been extensively evaluated in multiple phase 2 trials at 150mg s/c two weekly and 140mg SC 2weekly, respectively. At 12 weeks, the LDL-C was reduced by approximately 60 –79% at a trough and >90% at a peak [94]. The trials demonstrated good tolerability without drug-related side effects. Most of the clinical development of PCSK9 inhibitors took place in the phase-3 development programme.

1.8.3 Other therapies

Niacin has been said to raise the HDL-C dose-dependent manner by up to 25% to reduce the LDL-C by 15-18% and TG by 20-40%. The main study with nicotinic acid was of a slow-release formulation that included an additional agent used to alleviate the flash associated with niacin. However, the studies have shown no benefit but increased adverse events such as hyperuricaemia, increased blood glucose and liver dysfunction; thus, this drug has not been approved in Europe [95].

Fibrates work by agonising the peroxisome proliferator-activated receptor alpha via transcription factors, thus regulating gene expression in various lipid and lipoprotein metabolism steps. They have good efficacy in lowering triglyceride with a limited effect on LDL-C or HDL cholesterol. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, 5518 patients on simvastatin, between 40-79 years (mostly males),

were randomised to receive either placebo or Fenofibrate. The primary outcome rate of 2.2% on Fenofibrate vs. 2.4% on placebo was achieved. It was therefore concluded that there was no significance in primary outcomes between the two groups (HR in the fenofibrate group 0.92;95% CI 0.79 to 1.08, p=0.32). The Annual death rate was 1.56% in the Fenofibrate and 1.61% in the placebo group (HR 0.91 CI 95%:0,75 to 1.10. P=0.33). Further subgroup analysis noted an increased primary outcome rate of 38% in females and an 18% reduction in males; however, there were no other studies on female patients to compare such findings. On posthoc analysis of the 'dyslipidaemia subgroup' with high triglycerides and low HDL cholesterol, a primary outcome reduction rate of 17% in patients with baseline TG above 240mg/dl and HDL less than 34mg/dl was also achieved [96].

1.8.4 Predictors of failure of achievement of LDL-C targets

Factors associated with the attainment of LDL-C levels may vary according to different population groups and country income groups. In previous studies from low-and-middle-income countries, age, history of statin treatment, higher education levels, continuous therapy with lipid-lowering medications (compliance), and regular check-ups correlated with increased chances of reaching treatment targets, while diabetes and fast food consumption or obesity did not.[26, 97, 98, 99]

2. RATIONALE AND THE AIM OF THE STUDY

Mortality and morbidity from cardiovascular disease in South Africa have continued to rise over the years, and CVD currently ranks among the top 10 causes of mortality. However, little is known about the cardiovascular risk profile of patients in Sub-

Saharan Africa, and few studies have shown poor management of CVD risk factors[65]. There are new emerging drugs (PCSK/9 inhibitors) recommended for treating dyslipidaemia with high-risk CVD or patients with intolerance to statins which have been approved in other countries and are still in the process of being approved in others. However, their need has not been determined in the South African setting.

Therefore, the study aims to determine whether statin therapy, for secondary management of dyslipidaemia, in patients with coronary artery disease is adequate to achieve internationally recommended targets on patients attending the cardiac clinic at the Charlotte Maxeke Johannesburg Academic Hospital.

3. STUDY OBJECTIVES:

- To describe the demographics of patients presenting to CMJAH with angiographically proven ischemic heart disease by describing their baseline demographics, risk factors, medications, and biochemical parameters such as FBC, U&E, HIV, CRP, and Lipogram.
- To identify Very high cardiovascular risk patients with LDL-C levels that do not meet the international recommended target of 1.4 mmol/l and 50% absolute reduction from baseline LDL-C levels, despite maximal statin doses, which would benefit from Ezetimibe and PCSK9 inhibitors.
- To identify predictors of failure to achieve LDL-C targets.

4. METHODOLOGY

4.1 Eligibility criteria

1) The patients must have a history of prior acute coronary syndromes (STEMI/ NSTEMI/ UA/SA) with a supporting coronary angiogram confirming coronary artery disease.
2) The patients should have been on statins for at least six weeks, attending all follow-up visits and collecting treatment.

4.2 Exclusion criteria

1. Patients without prior coronary artery disease, however high cardiovascular risk (based on Framingham score 10-year cardiovascular risk score)
2. Patients with coronary artery disease not on lipid-lowering therapy or within six weeks

   of initiating lipid-lowering treatment or no follow-up lipograms post-CV event.
3. Patients who are taking oral anti-lipid therapy other than statins.

4.3 Study design

4.3.1 Patient selection:

The current study is retrospective and will analyse the lipid profiles, particularly LDL-C, of patients on statin therapy attending the cardiac clinic at CMJAH from the date of ethics approval. The sample size is 1000 patients, based on the Prevalence of CAD admissions in the Cardiology department At Johannesburg Hospital)

- Patients will require no consent as it will be a retrospective study.
- Files of patients with proven CVD will be retrieved from records (based on the angiogram reports obtained from the CCU database)
- Only files of patients meeting the inclusion/exclusion criteria will be used for the study.

4.3.2 Lipid analysis:

Venepuncture normally draws blood into a yellow collecting tube without an anticoagulant. Blood samples are normally drawn fasting. However,

According to the European Cardiology Society dyslipidaemia guidelines, TC, LDL-C and TG only vary by at most 0.3mmol after meals. Therefore, a non-fasting lipogram is now accepted for risk estimation.

The South African NHLS uses enzymatic, Colourimetric methods to measure TC, TG, and HDL-C using a Hitachi modular analyser and reagents supplied by Roche Diagnostic GmbH,

Manheim, Germany. LDL-C is then calculated using the Friedewald equation[100]. Friedewald formula for LDL-C is LDL-C = TC-HDL-C-(TG/2.2) mg/dl.

4.4 Data Analysis

Data will be captured on Redcap Software. STATA Version 15 (College Stateon, Texas) will conduct all statistical analyses. Categorical data will be represented as percentages. Normality tests (e.g., skewness and kurtosis) will be performed to ascertain the data distribution. Normally distributed data will be reported as means and standard deviations, and data with a skewed distribution as a median and interquartile range. For normally distributed data, parametric tests such as the paired student T-test will be used for continuous data and the Chi-square test for categorical data. For non-parametric continuous data, the Wilcoxon sum rank test will be used. A p-value of <0.05 will be employed as a threshold for statistical significance for all statistical tests.

5. ETHICS

No consent will be needed from patients as it is a retrospective study; however, an application to ethics for clearance and access of files from hospital management/DOH will be made.

6. LIMITATION

6.1. Limitations about retrospective studies, e.g., unable to ask patients about compliance with diet and medication.

6.2. Time

7. TIMELINE:

May 2019-May 2020

	May	June	July	August	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May/June
Literature review													
Protocol write-up													
Protocol assessment													
Ethics Application The application for approval by Hospital management													
Data Collection													
Data Analysis													
Paper write-up													

8. BUDGET AND FUNDING

Internet	R1000
Printing	R300
End note	R400
Research Methodology course and Africa Day Red Cap course	R700

9. SOURCE OF FUNDS

Self-funded

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ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms PM Ntila
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: patiencentila@gmail.com

CC: Supervisor: Drs N Tsabedze and D Mpanya <Nqoba.Tsabedze@wits.ac.za> and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/01/31

REF: *R14/49*

PROTOCOL NO: **M191183** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Secondary prevention and management of dyslipidaemia in patients with coronary artery disease on statin therapy in a tertiary academic centre in Johannesburg*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms PM Ntila

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M191183

NAME: (Principal Investigator)	Ms PM Ntila
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Secondary prevention and management of dyslipidaemia in patients with coronary artery disease on statin therapy in a tertiary academic centre in Johannesburg
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs N Tsabedze and D Mpanya
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/01/31

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

07/02/20
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

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LETTER OF SUBMISSION TO JOURNAL

Atherosclerosis Inbox - Google 31 March 2023 at 02:36

ATH-D-23-00373 - Confirming your submission to Atherosclerosis

To: Patience Ntila,

Reply-To: Atherosclerosis

Dear Melissa,

We have received your article "SECONDARY PREVENTION AND MANAGEMENT OF DYSLIPIDAEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE ON STATIN IN A TERTIARY ACADEMIC CENTRE IN JOHANNESBURG" for consideration for publication in Atherosclerosis. It has been assigned the following manuscript number: ATH-D-23-00373.

Your manuscript will be given a reference number once the submission has been checked and an Associate Editor has been assigned.

To track the status of your paper, please follow these instructions:

1. Go to: https://www.editorialmanager.com/ath/

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Thank you for submitting your work to Atherosclerosis.

Kind regards,

Editorial Manager
Atherosclerosis

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ath/login.asp?a=r). Please contact the publication office if you have any questions.

[redacted]

FACULTY OF HEALTH SCIENCES

PROTOCOL ASSESSORS MEETING

Candidate Full Name: P. Ntila

Student Number: 303796 Date: 3rd Sept 2019

School / Department / Division: Internal Medicine

1. Type of study *(tick all that apply)*:

- [x] Quantitative
- [ ] Qualitative
- [ ] Mixed Methods
- [ ] Laboratory
- [x] Clinical
- [ ] Other, please specify.....

2. Is title of the study appropriate *(preferably fewer than 20 words)*? (Yes) No

Comments: Misspelling - correct

3. Are the study objectives clear and linked to the research aim and title? (Yes) No

Comments:

4. Is the design of the study appropriate to meet the study objectives? (Yes) No

Comments:

11 March 2019/MP

5. **Are the proposed methods and tools appropriate to meet the research objectives?** (Yes) No

Comments: – state which guidelines you are using for LNL cut point (1.8mM)
– include data collection sheet with revised protocol

6. **Is the study feasible within the resources of:**
   a) The applicant? (Yes) No
   b) The department? (Yes) No
   c) The time frame? (Yes) No

– ask about compliance in data collection sheet
– data collection sheet is too extensive – is beyond scope of given study
– please cut back to only relevant questions that are in-line with study objectives

7. **If this is a PhD protocol assessment:** NO
   a) Is the content original? Yes No
   b) Does the content show the scope and depth of a PhD? Yes No

Comments:

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:
– exclude from data analysis subjects receiving anti-lipid therapy that are not statins
– check spreadsheet – make sure it is in consistent format.
– make sure all stats tests are tested correctly

ii. The appointment of the proposed Supervisor? (Yes) No

Nominee/s:

11 March 2019/MP

iii. The appointment of the proposed Co-Supervisor/s and/or additional co-supervisors? Yes / No

Nominee/s: _____

_____

_____

iv. Has the Chair of the Assessor Group signed the RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS form? Please attach. Yes / No

v. Has the Chair informed the student and supervisor about the Wits ethics requirements, and that if required, they must have either a Wits Human Research Ethics clearance certificate or a Wits Animal Research Ethics clearance certificate? Yes / No

vi. Based on the protocol provided (including any proposed changes by the protocol assessor group), does the student require:

1.	Human Research Ethics clearance certificate	Yes / No
2.	Animal Research Ethics clearance certificate	Yes / No
3.	No human or animal ethics certificate is required	Yes / No
4.	Unclear, will seek appropriate guidance from the HREC/AREC committees	Yes / No

vii. Has the Assessors chair, student and supervisor/s signed the ethics declaration form Yes / No

Overall recommendation regarding the protocol:

i. Revision of the protocol to the satisfaction of the Supervisor (**NB: if HoD approval is also required, please specify**): Yes / No
*(**Candidate**: one copy, list of corrections with page numbers and Supervisor approval letter – submit to PG Office).*

ii. Revision of the protocol to the satisfaction of the Assessor Group/Chair: Yes / No
*(**Candidate**: one copy, list of corrections with page numbers, Supervisor approval letter – submit to PG Office and PG Office to forward to the Assessor Group Chair).*

iii. Revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: Yes / No
*(**Candidate**: six copies, list of corrections with page numbers, Supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator / for PhD, all six copies to be submitted to the PG Office).*

iv. Candidate goes ahead (*no revision required*): Yes / No

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Details of Assessors:

Name:	Email:	Sign:
N. Gowther	nigel.gowther@nhls.ac.za	
Daksha Jivan	daksha.jivan@wits.ac.za	
Segwaya Llale	segwamatsosetsa@gmail.com	
DR DINNIE MOKGOKO	dr.mokgokc@gmail.com	

Details of Assessor Group Chair:

Name:	Email:	Sign:
N. Gowther		

Date: 3rd Sept 2019

11 March 2019/MP

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

DIVISION OF CARDIOLOGY

04 October, 2019

To whom it may concern:

Re: Dr Patience Mtwakazi Ntila, Student No. 303796N

This letter serves to notify that Dr Patience Mtwakazi Ntila has successfully addressed all MMed protocol assessment corrections and recommendations from the MMed assessor committee meeting. I am satisfied with her revised protocol.

Yours Sincerely

Dr Nqoba Tsabedze
Academic & Clinical Head - Division of Cardiology
Email: Nqoba.Tsabedze@wits.ac.za